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Effect of Microgravity on Living System

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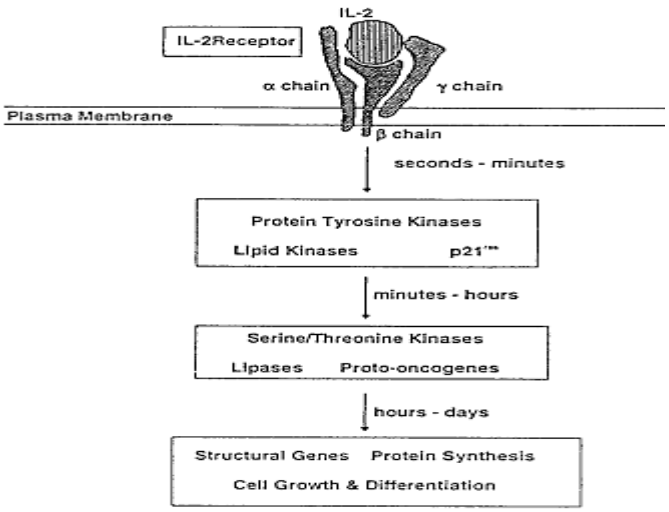
Abstract—Our planet Earth has been proliferating with life for billion years and life has survived in the constant influence ofgravity. So it's a major question if the gravity has an influence over the major processes and mechanisms of earth-inhabiting organisms and the environment. Since the first space missions and many ground-based experiments, it is a well established fact thatimmune cell function is severely suppressed in 0g, which makes the cells of the immune system an nobel model organism to investigate the influence of gravity on the cellular and molecular level.Also, it has been previously found that osteoblast growth is reduced and the ability to be activated to grow is significantly changed during a spaceflight. The lab of cell growth at University of California has studied gene growth andactivat ion of normal osteoblasts (MC3T3-E1) during spaceflight STS 76. The data suggests that quiescent osteoblasts are slower to enter the cell cycle in microgravity and that the lack of gravity itself may be a significant factor in bone loss in spaceflight. Thus, understanding the impact of gravity on cellular functions on Earth will provide not only important informations about the development of life on Earth, but also for therapeutic and preventive strategies to cope successfully with medical problems during space exploration. In this paper, we review the current knowledge about the question i.e. if and how cellular signal transduction depends on the existence of gravity.

I. Changed Immune responses in space

There have been evidences to altered immune responses and they were reported back in early 70's. These significant changes were entirely based on the data obtained from the crew members of Soyuz spaceships and of Skylab and Apollo [1,2]. A reduced level of reactivity of blood lymphocytes have been found in that. Also, a subclinical re-activation varicella zoster virus (VZV) has been found in astronauts [3,4]. It is a virus which becomes latent in the nervous system after primary infection, but is reactivated later frequently in immune suppressed individuals, such as after organ transplantation, and in patients with cancer or AIDS. T cell activation is one of the most interesting subjects here. Mainly because it regulates the key immune processes & failing which, causes irrepairable damages as is evident in the case of HIV infection. Whereas it is well known that gravity can be perceived by gravireceptors which are statocyst-like organelles or gravisensitive ion channels in the cell membrane in unicellular organisms such as Paramecium and Loxodes, where it strongly effects intracellular cell to cell communication and behaviour [5,6], the molecular mechanisms of gravisensitivity in mammalian cells are not properly known yet. It has been found after the pioneering discovery of Cogoli et al. at the first Spacelab-Mission 20 years ago [7], that proliferative response of lymphocytes after mitogenic stimulation is suppressed in zero gravity[8]. It has been significantly indicated by several Space & earth-based simulations that signal transduction cells are greatly affected by 0g e.g. T-lymphocytes.



Alteration in Cell-to-Cell communication in 0g.

Various studies have reported alterations in signal transduction in lymphocytes. In lymphocytes, 0g affected the protein kinase C [11,12] whereas delivery of first activation signal, patching and capping of conA-binding membrane proteins have been found to occur normally in spaceflight [13]. These findings point out the existence of gravisensitive cellular targets upstream from PKC and downstream from the TCR/CD3. Also, the DNA array analysis of T cells under simulated microgravity provided by RPM showed an alteration of various signal moduls, in specific NF-kB and MAPK-signaling [14]. Also the expression of some of the early oncogenes is inhibited during spaceflight [15].

0g has also been found to affect the monocyte function. There are significant proofs including lose of capability to secret IL-1 in monocytes during the spacelab-mission SLS-1 and of expressing IL-2-receptor [26]. Kaur et al . [19] prepared some control groups and then investigated monocytes isolated from astronauts before and after a. A marking reduction in phagocytosis, oxidative burst and degranulation-capacity was revealed. Meloni et al . [20] have recently demonstrated that simulated weightlessness results into huge alterations in the cytoskeleton of monocytes, which in turn affects motility and a severe reduction in the locomotion ability of monocytic cells in microgravity [21].

[1]. **Cell migration in 0g.**

Neutrophil locomotion is important for immune effector function and mechanism, because the cells have to leave the blood vessels and migrate to the places of infection and injury to accomplish their main task of phagocytosis. They are among the most important cells regulating the immune response, because they can influence both the stages of immune reactions i.e. the induction and effector stages. Several research studies have provided evidence of a disturbed function of neutrophil granulocytes viz. astronauts of spaceflight missions when returned exhibited a strong increase in neutrophil granulocytes just after the landing [23,24], and neutrophil chemotactic assays revealed a 10-times decrease in the standard dose-response after landing [25].

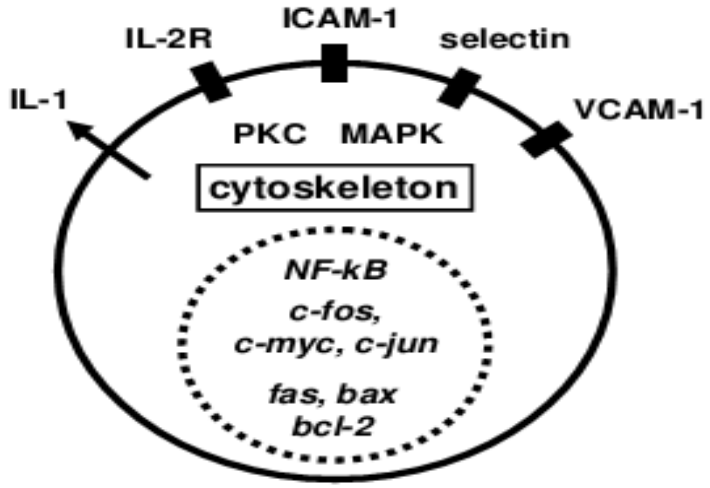


Figure 1
Gravi-sensitive signal transduction elements in mammalian cells. Gravi-sensitive signal transduction elements has been detected at the cell surface, such as VCAM-1 (Vascular cell adhesion molecule 1), ICAM-1 (Intercellular adhesion and molecule 1) and IL-2R (interleukin-2 receptor), in the cytoplasma such as PKC (protein kinase C) and MAPK (mitogen-activated protein kinases) and in the nucleus such as expression of c-fos, c-jun and other genes. Microgravity severely affects also the cytoskeleton. However, the primary molecular mechanisms how microgravity influences cell signaling are unknown.

The cytoskeleton is plays a role in for providing a cell its shape and for generating the forces required for cell motility. It is an internal network of at least three different types of cytosolic fibers: actin filaments, then the microtubules and finally intermediate filaments. Actin is one of the most highly conserved and abundant eukaryotic proteins which is constantly polymerized and depolymerized to invoke cellular motility, tissue formation and repair within cells [32,33]. It has been shown to be important for the migration of T lymphocytes and also for neutrophil granulocyte migration. On the contrary, an intact microtubule network doesn't appear to be essential for neutrophil migration as the drugs such as colchicine that is a microtubule-disrupting drug.

Influence Of Micro-Gravity On Cytoskeleton

Multiple researchers have shown that this complex network of fibers is susceptible to some environmental factors such as 0g and altered gravitational forces [37]. Few studies have shown the alteration in the actin and microtubule cytoskeleton in microgravity. A 2D-clinorotation provided a few minutes of simulated weightlessness and a affect in the cytoskeleton of lymphocytes, astrocytes, neurons and glial cells, disorganizing microtubules, intermediate filaments and microfilaments was witnessed[38,39]. A change in the morphology of actin and microtubule components of cytoskeleton have been observed in 0g: both simulated and the real one. Gruener and Hughes-Fulford showed that reorganization in actin fibers gave a response to the gravity level and showed unusual assembly of actin stress fibers during spaceflight [41-43]. Other studies have provided the evidences that micro-tubules are gravity sensitive, too [45]. Microtubule self-assembly is restricted in the absence of gravitational force in space [46], and Lewis et al. have observed that the microtubule component extended from a roughly defined centrosome in Jurkat cells in human [40]. Further, cancer cells grown under 0g showed an increased response and highly dis-organized vimentin and also altered microtubules [47,48].

With regard to migration, neutrophils are the fastest moving cells at all with a speed maximum of 15 to 20 μm/min [49], and the starting signal for their navigation to sites of inflammation is provided by the early proinflammatory cytokines such as the bacterial peptide fMLP [50] which is the major chemotactic peptide produced by E. coli and have known to be a strong stimulator for the navigation of neutrophil granulocytes. fMLP has a role in binding and activating a class of G-protein-coupled receptors. This binding of ligand results in the activation of two signalling pathways: (i) the activation of the PLC-gamma results in the formation of inositol-1,4,5-phosphate (IP_3) and diacylglycerol (DAG), this mediates a IP 3 mediated release of intra-cellularly stored calcium in the ER and activation of the protein kinase C (PKC) which is DAG-mediated. [50-52].(ii) the activation of the adenylyl cyclase results into an increase of cytosolic cAMP, which leads to an activation of calcium ATPase (SERCA) pump and calcium sequestration. Thus, when neutrophils stimulate fMLP activates a signal transduction pathway leading to an increase in the level of of cytosolic calcium which has been shown to be necessary for the successive development of actin-based migration [53]. Moreover, observations of migrating neutrophils within a 3D collagen matrix have revealed a frequent elevation in the level of calcium in those parts of the cells that had underwent some shape changes a few seconds later, and visualization of the calcium signal was demonstrated as a directional marker for the orientation of neutrophils navigating in a 3D space [50].

Changes in gene expression caused by low gravity forces:

Since life on Earth evolved in a 1-G environment, it was a hypothesis that gravity itself may have an effect on bone growth. The data obtained before the space-flight has focused on the alterations in growth that may be due to the non-existence of gravity. In the ground experiments on STS-76, the MC3T3-E1 osteoblasts on coverslips placed in Biorack plunger boxes were grown in a serum deprived. The cells were subjected to 3-G gravity for 8 minutes. It is known that PGE_2 and PGI_2 are released during exercise, therefore indicating that the same pathway may get applied in bone loss occurring in 0g.

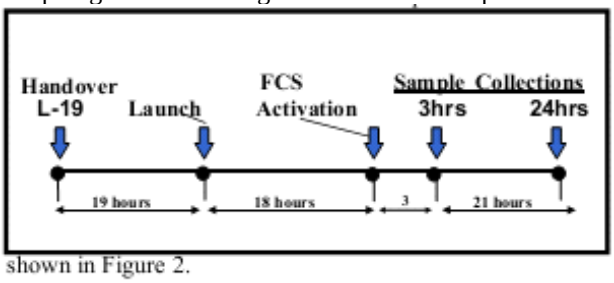


Figure 1: Timeline for Osteo experiments

shown in Figure 2.

Arabidopsis Thaliana in micro-gravity: Perception of Gravity, Signal Transduction and Graviresponse in Higer plants

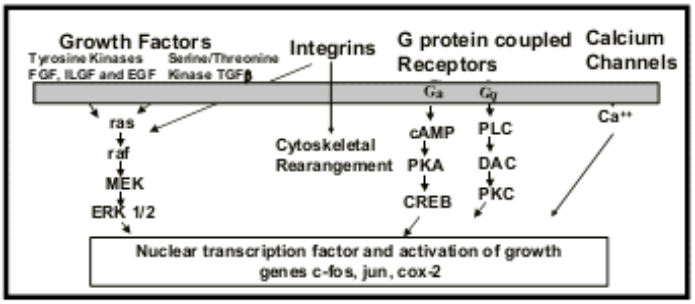
Nasa has planned to carry out a research on the activity of a higher plant i.e. A. Thaliana in 0g under the investigation of Alexander Dovzhenko et al.The aim of the proposal is to unequivocally identify genes that are activated, or in some way regulated, by gravity. This knowledge can have an impact on practical agronomic purposes, e.g. architecture of root and shoot systems as well as realizing this potential for regulating plant growth in space. Significant interest and support from industry is demonstrated, especially in the analytical genomic sector. The project will use state-of-the-art tools to evaluate the architecture of these pathways. Using DNA microchips and other molecular genetic technology we will gain new quantitative and qualitative information on gravity-regulated gene expression.

The experiments will study the well-known flowering plant, *Arabidopsis thaliana*, also known as mouse-ear cress or thale cress, a plant which is genetically related to soybeans, cotton, vegetables and oil seed crops. A. thaliana has all of the normal plant functions, and has become a useful research model. Some of its advantages are its short life cycle, small size, prodigious seed production, and its small genome of about 110 Mb comprising 25.498 genes.

Low levels of gravity for a short period cause changes in gene expression:

A small magnitude mechanical loading , like during a Space Shuttle launch, can change mRNA levels in early osteoblastic cells (54). Alterations in gene expression due to mechanical force of gravity can be caused by several parts of the cell. The mechanisms by which mammalian cells react to gravitational signals are still not known. Although, it is known that there are several mechano transducers seen in Figure 2 in the cell that may be held responsible.

Figure 2. Possible pathways for mechanotransducers



Quiescent or early cells for changes depending on gravity in mRNA levels for 9 genes involved in growth of bone cell and maturation were tested. Analyses of osteoblast gene expression demonstrated a reduced induction of TGF β , bFGF, c-myc, bcl2 and PCNA in microgravity. The initial FCS induction of cox-2 was decreased in 0g although the production of PGE2 was elevated in the 1-G samples. It was found that when compared to 1-G controls, cox-2 mRNA is decreased in the 0-G samples. The copy number for cox-1 mRNA was too low to detect. This would suggest that since cox-2 is depressed in the microgravity samples, the cells subjected to the 0-G environment did not enter the growth phase of the cell cycle.

	Relative to GR 3 hours		Relative to GR 24 hours	
Gene	0G	1-G	0-G	1-G
TGFβ	↓	=	...	...
PCNA	↓	↓	...	...
FGFb	↓	↓	...	...
BCL2	↓	↓	↓	↑
EGFr	=	=	=	=
c-myc	↓	=	...	...
Cyclin A	↓	↓	↓	↓
Cyclin E	=	=	↓	↓
Cox-2	↓	=	↓	~=
cPLA2	↓	=	...	...
PGE_2	↑	↑	↑	↑

TABLE 1: Relative expression in orbit compared to ground control. ... no samples tested;
= equivalent to control; ↑ increased relative to control;
↓ decreased relative to control

Also, the deLaat 's group have demonstrated that the nuclear reactions to protein kinase C signal transduction were sensitive to alterations in the levels of gravity (55). They demonstrated that EGF and phorbol ester (TPA) induced gene expression of c-fos and c-jun were altered by 0g, while the calcium response wasn't changed, thus pointing out the diacylglyceride (DAG) portion of the PKC cell-to-cell communication.

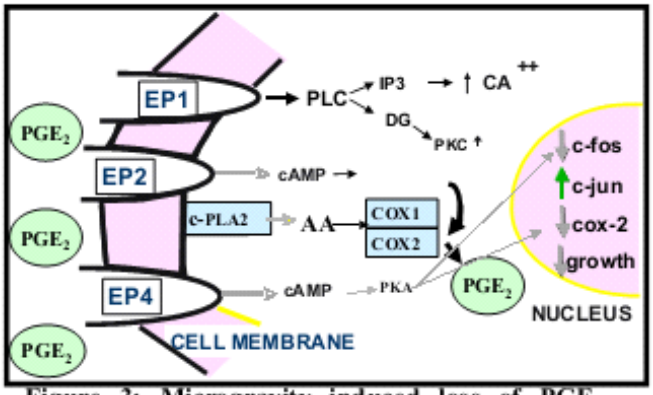


Figure 3: Microgravity induced loss of PGE_2 signaling pathway in microgravity It is possible that changes in the PGE_2 receptors could inhibit recognition of PGE_2 in microgravity. As seen in the figure above, if PGE_2 were unable to bind to the EP receptors, this would result in a high level of PGE_2 in the media and an inhibition of signaling through the 7-domain transmembrane G-coupled prostaglandin receptor pathway (shown in gray lines).

Thus, it was shown after all these studies that 0g i.e. lack of mechanical stress changes prostaglandin content, prostaglandin-response, morphological changes and gene expression in osteoblasts. It is likely to happen that lowered level of gravity induced mechanical stress coupled with other changes in cell-to-cell communication directly contribute to astronaut bone loss during spaceflight. It has been shown that blocking the prostaglandin signaling pathway can restrict formation of new bone in humans both in vivo and in vitro (56, 57). In these studies it has been demonstrated that 0g causes inhibition of fetal calf sera stimulation of mRNA in 8 of 9 genes deeply studied. Simulated gravity was able to restore message levels to normal in 5 of the 8 inhibited messages. These data suggest that simulated gravity may compensate the loss of bone in astronauts in spaceflight to enable mankind to go to Mars.

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